EXHIBIT 7

U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Division of Drug Marketing, Advertising and Communications

Frequently Asked Questions (FAQs)

Click on a topic to link to questions and answers.

Consumer-Directed Advertisements

What are the general requirements for prescription drug advertisements directed toward consumers?

The same statute and regulations apply regardless of the audience targeted by a prescription drug advertisement. The Federal Food, Drug, and Cosmetic Act (the act) requires that all drug advertisements contain (among other things) information in brief summary relating to

side effects, contraindications, and effectiveness. Because of this statutory wording, this requirement has become known as the Brief summary. The current advertising regulations specify that this information disclosure needs to include **all** the risk information in a product's approved labeling. Typically, print advertisements will include a reprinting of the risk-related sections of the product's approved labeling (also called full prescribing information or the package insert). Sponsors, however, can write this risk information in language appropriate for the targeted audience; FDA encourages this approach.

In addition to the specific disclosure requirements, advertisements cannot be false or misleading or omit material facts. They also must present a fair balance between effectiveness and risk information. FDA has consistently required that appropriate communication of effectiveness information includes any significant limitations to product use.

How do prescription drug broadcast advertisements differ from print advertisements?

Current regulations specify two requirements that all prescription drug broadcast advertisements must meet. First, broadcast advertisements must include the product's most important risk-related information in the audio or audio and visual parts of the advertisement. This is sometimes called the major statement. This requirement is not addressed by the guidance. Second, broadcast advertisements must contain either a brief summary of the advertised product's risk information, or alternatively, make adequate provision for disseminating the product's approved labeling in connection with the ad. Thus, the regulations for broadcast advertisements recognize broadcast's inherent limitations by providing an alternative mechanism for meeting the act's information disclosure requirement.

What needs to be included as part of the major statement requirement?

The major statement must include all of the most important risk information related to the product. Because risks vary from product to product, the amount of information disclosed for any particular product to meet this requirement will vary as well.

How does a product's brief summary differ from its approved labeling?

The brief summary is generally shorter -- sometimes significantly so. The brief summary typically includes only the risk-related sections of the product's labeling. This is because the advertising text itself generally meets the requirement for including effectiveness information by giving the product's indication (i.e., what it is used for), and any limitations concerning how and when the product should be used. In contrast, product labeling includes non-risk-related information, including all effectiveness information (sometimes even about the clinical studies used as the basis for product approval), how it should be taken (dosage information), how the drug product is supplied (e.g., the quantity of drug in each pill), and information about how the product works in people's bodies.

Does FDA intend to do anything about the brief summary information? I've heard a lot of concerns about its value for consumers.

FDA has also heard concerns about the lack of value of the required information from some individuals and groups. It has heard from others that consumers should get full disclosure

of risk information. The agency intends to address these concerns fully through the rulemaking process. In the interim, the agency encourages product sponsors to provide consumers with nonpromotional, consumer-friendly information consistent with product labeling, along with the information required by the act and the regulations. As mentioned above, in the case of print advertisements, FDA encourages sponsors to write their product brief summaries in consumer-friendly language.

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Drug of Choice

May the phrase "drug of choice" be used in advertising or labeling?

The phrase "drug of choice," or any similar phrase or presentation, used in an advertisement or labeling would make a superiority claim and, therefore, the advertisement or labeling would require substantial evidence to support that claim.

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Drug Name Size

Does the full prescribing information or the brief summary type have to be any particular size?

No, but the regulations specify size in sections 201.10(g)(2) and 202.1(b)(2) which state: "The established name shall be in printed letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features."

Does "half as large" refer to point size or actual type size?

DDMAC has interpreted "half as large" to be actual size, not point size, of upper and lower case letters in the proprietary and established drug names.

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"FDA-Approved"

May an advertisement or labeling piece include the phrase "FDA approved"?

Yes, if the manufacturer or sponsor has received a letter stating that the product has been approved. Effective on the date of implementation, the Food and Drug Administration Modernization Act of 1997 eliminated Section 301(l) of the Federal Food, Drug, and

Cosmetic Act that prohibited "The using . . . of any representation or suggestion that approval of an application with respect to such drug or device is in effect . . . ."

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"New"

How long may the word "new" be used in promotional labeling and advertisements for a newly approved product, indication, or dosage form?

DDMAC generally considers that "New" is an accurate description of the marketing phase for six months from the time a product is initially marketed. This should be distinguished from the time the product is cleared by FDA for marketing.

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Package Inserts

Does it matter where a package insert is placed on a labeling piece, such as on a calendar or a brochure with a pouch?

The package insert can be anywhere as long as the labeling piece states clearly where the package insert is located and as long as the package insert accompanies the piece.

Are package inserts required in all labeling pieces for products that are the same except for different strengths or dosages?

Yes. Even though products may be very similar, package inserts may be different for different dosage forms or different delivery systems for the same drug. The regulations would require a package insert for each dosage form and delivery system for which claims appear in the promotional labeling piece. Some drug products, however, have multi-dosage form package inserts. In those cases, the same package insert could be attached to each piece, even if the dosage forms or delivery systems were different.

Does a package insert in another language also have to be submitted in English?

Yes. Package inserts have to be submitted in English and not only in the foreign language.

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Postmarketing Reporting

Where do the regulations state the requirement for submitting prescription drug advertisements and labeling?

Under 21 C.F.R. 314.81(b)(3)(i):

> **Section 314.81 Postmarketing reports.**
>
> *****
>
> (b) *Reporting requirements*. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:
>
> *****
>
> (3) *Other reporting--(i) Advertisements and promotional labeling.* The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product . . . .

(See Selected Provisions of the Act and Regulations for the entire paragraph.)

When do promotional materials need to be submitted to DDMAC?

Pursuant to 314.81(b)(3)(i), submissions must be made " . . . at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product."

Do all promotional materials for prescription drugs have to be submitted to DDMAC?

The regulations for submitting materials apply to holders of NDAs, ANDAs, and antibiotic applications. Manufacturers of pre-1938 products and products that have declared "not new drugs" are not required to submit specimens. All products have labels and prescribing information, however, and products without approved labeling have permitted labeling. Permitted labeling indicates FDA agrees with the label or labeling and permits its use. A manufacturer of a product with permitted labeling is responsible for assuring that advertisements and promotional labeling pieces are consistent with the product labeling.

What form should applicants use to submit materials to FDA?

Form FDA 2253 Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use.

How can I obtain an Form FDA 2253?

Address

To whom should I send the materials?

Two copies of all materials should be sent to:

Division of Drug Marketing, Advertising, and Communications
5600 Fishers Lane, HFD-40
Rockville, MD 20857

Upon arrival, the material will be logged in for tracking and assigned to a reviewer in DDMAC.

Who is responsible for submitting a Form FDA 2253 if the manufacturer and distributor are different companies?

Either company may submit the specimens, however, the applicant is ultimately responsible for compliance with 21 CFR 314.81(b)(3).

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Presentation of Information

Can the layout or the way information is presented affect whether an advertisement or labeling piece is in compliance with the regulations?

Yes, 21 CFR 202.1(e)(7)(viii) states that an advertisement may be false, lacking in fair balance, or otherwise misleading if it:

"Fails to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis."

For example, the presentation below of the word benefits and the word disadvantages would not be considered comparable. Although the words are the same point size, the color and contrast with the background make the word benefits much more noticeable than the word disadvantages.

BENEFITS disadvantages

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Pre-distribution Submissions

Does FDA approve advertisements and promotional labeling before use by the company?

No, except for accelerated approval products and, in rare instances, when FDA may require pre-approval of promotional materials as part of an enforcement action. However, DDMAC provides opinions on proposed advertisements and labeling pieces before use upon request by an applicant.

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Reminder Advertisements and Labeling

What is a reminder advertisement?

Under 202.1(e)(2)(i), reminder advertisements are identified as an exemption to the advertisement regulations, including the provisions under 202.1(e) to provide a brief summary. Reminder advertisements " . . . call attention to the name of the drug product but do not include indications or dosage recommendations for use of the drug product. . . . and, optionally, information . . . containing no representation or suggestion relating to the advertised drug product." Reminder advertisements cannot make a representation about the product or suggest a use for the product.

What is reminder labeling?

Under 201.100(f), reminder labeling is " . . . labeling which calls attention to the name of the drug product but does not include indications or dosage recommendations for use. . . . and, optionally, information . . . containing no representation or suggestion relating to the drug product." Reminder labeling is exempted from the provisions under 201.100(d) to provide the full prescribing information.

Can a reminder advertisement compare one product to another or say one product is an alternative for another?

No. Such a comparison would imply the indication, and then the advertisement would no longer meet the exemption criteria.

Does FDA limit the amount of money that can be spent on reminder advertisements or reminder labeling pieces or regulate the types of objects (such as pens, cups, calendars, etc.) that can be used as reminder advertisements or reminder labeling pieces?

FDA regulations do not limit how much money companies may spend on reminder advertisements and labeling pieces, nor do the regulations limit the types of objects that can be used. The regulations, however, limit the type of information that can be presented in reminder advertisements and labeling pieces, and not just the written information, but information that may be portrayed though graphics, design, or some other visual representation.

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Miscellaneous Questions

Are the advertising and labeling procedures for orphan drugs and regular NDA products the same?

Yes.

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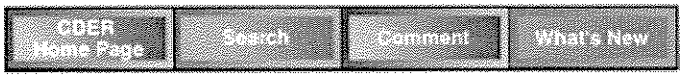

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Revised Wednesday, May 28, 2003

EXHIBIT 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Cary Rayment, President and Chief Executive Officer
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

Re: NDA 20-805
CIPRO® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension)
MACMIS # 13122

WARNING LETTER

Dear Mr. Rayment:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the Alcon website (URL: http://www.alconlabs.com/us/aj/products/RxTher/CiproHC_ProdPRO.jhtml) for CIPRO® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) through routine monitoring and surveillance. The website is misleading because it makes unsubstantiated superiority claims, fails to reveal important risk information associated with the use of CIPRO® HC OTIC, and overstates the efficacy of the drug. Therefore, the website misbrands CIPRO® HC OTIC within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) & (n), 321(n), and FDA implementing regulations. See 21 CFR 202.1(e)(5)(i).

DDMAC has previously objected, in an untitled letter dated July 18, 2003, to your dissemination of CIPRO® HC OTIC promotional material that made unsubstantiated superiority claims, omitted important risk information, and overstated the efficacy of the drug. We are concerned that you are continuing to promote CIPRO® HC OTIC in a violative manner.

Background

The Indications and Usage section of the approved product labeling (PI) for CIPRO® HC OTIC states:

> **"CIPRO® HC OTIC is indicated for the treatment of acute otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Proteus mirabilis*."**

CIPRO® HC OTIC is associated with several important contraindications, warnings, and precautions. For example, the PI for CIPRO® HC OTIC contains the following important risk information:

CONTRAINDICATIONS

CIPRO® HC OTIC is contraindicated in persons with a history of hypersensitivity to hydrocortisone, ciprofloxacin or any member of the quinolone class of antimicrobial agents. This nonsterile product should not be used if the tympanic membrane is perforated. Use of this product is contraindicated in viral infections of the external canal including varicella and herpes simplex infections.

WARNINGS

NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.
CIPRO® HC OTIC should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first does, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

PRECAUTIONS

GENERAL: If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment.

Unsubstantiated Superiority Claims -- Efficacy

Your website implies that CIPRO® HC OTIC provides faster relief of the pain associated with acute otitis externa than other available treatment options. For example, the following claims appear on the first page of your website:

- "What a difference a day makes."
- "YOU DON'T WANT 19 EXTRA HOURS OF THIS. OR OF OTITIS EXTERNA."
- "CIPRO® HC OTIC Ends The Pain 19 Hours Sooner"

These claims suggest that use of CIPRO® HC OTIC is superior to other products in the treatment of otitis externa in that it ends the pain 19 hours sooner. Your website does not specify what comparison products require 19 additional hours to "end pain." There is, however, a footnote that contains a reference for a clinical trial conducted by Pistorius et al.[1], the description of which indicates that the trial compared CIPRO® HC OTIC and an investigational otic preparation of ciprofloxacin alone to an otic suspension of polymyxin B-neomycin-hydrocortisone (Cortisporin). The website also contains the following reference at the end of the section entitled "Combination Strength Delivers Results" -- "**Clinical success defined as resolution and improvement in a controlled, nonblinded, multicenter U.S. trial comparing CIPRO® HC OTIC with a polymyxin B-neomycin-hydrocortisone combination [Cortisporin] in patients with acute otitis externa." The description of this reference fails to mention that the trial also compared CIPRO® HC OTIC to an investigational otic preparation of ciprofloxacin alone.

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[1] Pistorius B, Westberry K, Drehobl M, et al. Prospective, randomized, comparative trial of ciprofloxacin otic drops, with or without hydrocortisone, vs. polymyxin B-neomycin-hydrocortisone otic suspension in the treatment of acute diffuse otitis externa. *Infect Dis in Clin Pract.* 1999;8:387-395.

The claims, together with the references, suggest that CIPRO® HC OTIC ends ear pain 19 hours sooner than Cortisporin (the referenced polymyxin B-neomycin-hydrocortisone combination) and ciprofloxacin alone. While it is true that CIPRO HC OTIC ends pain 19 hours sooner than ciprofloxacin alone, it does not end pain 19 hours sooner than Cortisporin. In fact, in the trial that is referenced, CIPRO® HC OTIC and Cortisporin were not statistically significantly different in their effect on ear pain. The difference in time to end ear pain in the trial of CIPRO HC OTIC® and Cortisporin was 7 hours. FDA is not aware of substantial evidence or substantial clinical experience to support the 19-hour claim. Therefore, these claims are false or misleading in that they suggest that CIPRO® HC OTIC ends pain 19 hours sooner than Cortisporin. It should be noted that FDA found this trial (Pistorius et al.) to be inadequate to support such claims in a previous untitled letter dated July 18, 2003.

Failure to Reveal Important Risk Information

Your website fails to reveal material facts in light of representations made and with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the main part of the website presents numerous effectiveness claims for CIPRO® HC OTIC, such as:

1. "What a difference a day makes."
2. "YOU DON'T WANT 19 EXTRA HOURS OF THIS. OR OF OTITIS EXTERNA."
3. "CIPRO® HC OTIC Ends The Pain 19 Hours Sooner"

Your website fails to present <u>any</u> risk information within the body of the main CIPRO® HC OTIC page on the website. One must navigate to other pages titled "CIPRO HC Otic Comparative Information," "CIPRO HC Otic Prescribing Information," and "Frequently Asked Questions / Contact Us" to obtain risk information. Furthermore, once the viewer reaches the "CIPRO HC Otic Comparative Information" page, the risk information is listed at the end of the page without any headers or other signals to indicate to the reader that it is important risk information. The website therefore misleadingly fails to reveal important risk information necessary for context on the pages containing information about the efficacy of CIPRO® HC OTIC, including the following important Contraindication and Warning information:

> CIPRO® HC OTIC is contraindicated in persons with a history of hypersensitivity to hydrocortisone, ciprofloxacin or any member of the quinolone class of antimicrobial agents. This nonsterile product should not be used if the tympanic membrane is perforated. Use of this product is contraindicated in viral infections of the external canal including varicella and herpes simplex infections.
>
> **NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.**
> CIPRO® HC OTIC should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first does, have been reported in patients receiving systemic quinolones.

> Serious acute hypersensitivity reactions may require immediate emergency treatment.

Furthermore, in the main body of the CIPRO HC Otic page on the website you fail to include important precautions such as "If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment." The failure to present this important risk information may lead to serious health risks because failure to improve may represent a fungal superinfection or a resistant bacterial infection.

Overstatement of Efficacy

Your website includes the claims "Fewer drops to total pain relief" and "Shorter course to total pain relief." These claims are misleading because they overstate the efficacy of CIPRO® HC OTIC. The phrase "total pain relief" suggests that patients have 100% pain relief when using the product. FDA is not aware of substantial evidence or substantial clinical experience demonstrating 100% pain relief. We note that in the Pistorius et al. study cited on the website, CIPRO® HC OTIC had a clinical response rate at the end of therapy (defined as resolution of infection or improvement) of 90%. Resolution of infection or improvement of 90% is not evidence of "total pain relief." Therefore, the phrase "total pain relief" is misleading because it overstates the efficacy of CIPRO® HC OTIC.

Conclusion and Requested Action

Your website makes unsubstantiated superiority claims, fails to reveal important risk information included in the labeling of CIPRO® HC OTIC, and overstates the efficacy of the drug in violation of 21 U.S.C. §§ 352(a) & (n), 321(n); 21 CFR 202.1(e)(5)(i).

DDMAC requests that Alcon immediately cease the dissemination of violative promotional materials for CIPRO® HC OTIC such as those described above. Please submit a written response to this letter on or before May 11, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for CIPRO® HC OTIC such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 13122 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for CIPRO® HC OTIC comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

EXHIBIT 9

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Mr. Michael W. Bonney
President & CEO
Cubist Pharmaceuticals
65 Hayden Avenue
Lexington, MA 02421

Re: NDA # 21-572
Cubicin™ (daptomycin for injection)
MACMIS # 12433

WARNING LETTER

Dear Mr. Bonney:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ad) for Cubicin™ (daptomycin for injection), submitted by Cubist Pharmaceuticals (Cubist) under cover of Form FDA 2253. The ad fails to reveal important risk information associated with the use of Cubicin and, therefore, misbrands the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. See 21 U.S.C. 321(n), 352(n); 21 C.F.R. 202.1(e)(3)(i). Additionally, DDMAC has reviewed promotional statements for this drug that appear on a website (URL: http://www.cubicin.com) maintained by Cubist, and also submitted on Form FDA 2253. The website is misleading because it broadens the indication for Cubicin, fails to reveal important risk information associated with the use of Cubicin, and makes an unsubstantiated comparative claim. Therefore, the website misbrands Cubicin. See 21 U.S.C. 321(n), 352(a), (n). Your broadening of the indication for Cubicin and failure to reveal important risk information associated with the use of Cubicin poses serious public health and safety concerns because the inappropriate use of Cubicin can result in therapeutic failure, and increases in morbidity and mortality in infections for which Cubicin has not been proven safe and effective.

Background

The Indications and Usage section of the approved product labeling (PI) for Cubicin states:

> "CUBICIN (daptomycin for injection) is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms (see also **DOSAGE AND ADMINISTRATION**): *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimillis* and *Enterococcus faecalis* (vancomycin-susceptible strains only). Combination therapy may be clinically indicated if

the documented or presumed pathogens include Gram-negative or anaerobic organisms (see **CLINICAL STUDIES**).

Daptomycin is not indicated for the treatment of pneumonia.

Cubicin is associated with several important contraindications, warnings, precautions, and adverse events. For example, the Precautions section of the PI for Cubicin contains the following important risk information:

> "***Skeletal Muscle:*** In Phase 3 complicated skin and skin structure infection (cSSSI) trials, elevations in serum creatine phosphokinase (CPK) were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 10/558 (1.8%) comparator-treated patients. Skeletal muscle effects associated with daptomycin were observed in animals (see **ANIMAL PHARMACOLOGY**).
>
> Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. CPK levels should be monitored weekly in patients who receive CUBICIN. Patients who develop unexplained elevations in CPK while receiving daptomycin should be monitored more frequently. Among patients with abnormal CPK (>500 U/L) at baseline, 2/19% (10.5%) treated with CUBICIN and 4/24 (16.6%) treated with comparator developed further increases in CPK while on therapy. In this same population, no patients developed myopathy. Daptomycin-treated patients with baseline CPK >500 U/L (n=19) did not experience an increased incidence of CPK elevations or myopathy relative to those treated with comparator (n=24).
>
> CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1000U/L (~5x ULN), or in patients without reported symptoms who have marked elevations in CPK (≥10x UNL). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving CUBICIN."

Broadening of Indication

Your website implies that Cubicin is safe and effective, and FDA-approved, for the treatment of all infections caused by *Staphylococcus aureus* (including methicillin-resistant strains).

For example, the following claims appear on the first page of your website:

- "CUBICIN is the only once-daily, rapidly bactericidal antibiotic proven effective against both MRSA [methicillin-resistant Staphylococcus aureus]and MSSA [methicillin-susceptible Staphylococcus aureus]"
- "Serious against Staph"
- "Proven clinically successful against MRSA and MSSA"
- "Bactericidal against MRSA and MSSA"
- "Once a day—the only QD agent approved for treatment of MRSA and MSSA"

These claims are misleading because they imply that Cubicin is safe and effective, and FDA-approved, for all infections caused by MRSA and MSSA (e.g., endocarditis and pneumonia), when this has not been demonstrated by substantial evidence or substantial clinical experience. The PI specifically states that Cubicin is indicated for "the treatment of complicated skin and skin structure infections [cSSSI] caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimillis* and *Enterococcus faecalis* (vancomycin-susceptible strains only) (emphasis added). Also, the PI specifically states that "Daptomycin is not indicated for the treatment of pneumonia" (emphasis added). The Adverse Reactions section of the PI also describes an important reason for this limitation: "In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events" (emphasis added).

FDA is not aware of substantial evidence or substantial clinical experience to support the efficacy of Cubicin in non-cSSSI infections. Blurring the distinction between cSSSI and non-cSSSI infections by statements that combine and generalize all *Staphylococcus aureus* infections, such as "Proven clinically successful against MRSA and MSSA," and suggesting that Cubicin is proven safe and effective, and approved by FDA, to treat all such infections is misleading and poses a significant public health risk because such practice could lead to therapeutic failure and death.

Failure to Reveal Important Risk Information

The ad and website fail to reveal material facts in light of representations made and with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the main part of the ad presents effectiveness claims for Cubicin, such as "New AGAINST STAPH" and "The only once-daily bactericidal antibiotic---with a distinct mechanism of action---proven effective against both MRSA and MSSA," but fails to provide any risk information. For example, you fail to include information on the risk of increased CPK levels and the risk for development of muscle pain or weakness, which is described in the precautions section of the PI for Cubicin. This information is necessary to qualify the effectiveness claims appearing in the main part of the ad. The main part of the ad includes a reference to the brief summary of prescribing information; however, this statement is not sufficient to provide the appropriate qualification or pertinent information for the claims made in the main part of the ad. See 21 CFR 202.1(e)(3)(i).

The website is similarly misleading because it fails to reveal important risk information necessary for context on pages containing information about the efficacy of Cubicin. For example, you fail to include information on the risk of increased CPK levels and the risk for development of muscle pain or weakness, which is described in the Precautions section of the PI for Cubicin.

DDMAC had previously objected, in an untitled letter dated November 22, 2000, to your failure to disclose facts that are material in light of the representations made in promotion about CUBICIN. Specifically, Cubist failed to disclose important risk information about Cubicin on your website. We are concerned that you are continuing to promote Cubicin in a similarly violative manner.

Misleading Comparative Claim

Promotional materials are false or misleading if they suggest that a drug is superior to other products when such has not been demonstrated by substantial evidence or substantial clinical experience. Your website includes the claim "Bactericidal antibiotics are generally regarded as superior to bacteriostatic agents for the treatment of most infections." This claim implies that, because Cubicin is a bactericidal antibiotic, it is superior to other antibiotics intended for the same conditions when such has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, as noted in the Adverse Reactions section of the PI and previously described, Cubicin was determined to be inferior to comparator agents in the treatment of CAP. FDA is not aware of substantial evidence or substantial clinical experience to support the superior efficacy of bactericidal antibiotics compared to bacteriostatic agents. Furthermore, the statement in your website, "However, clinical data to support this position are lacking except in specific indications," does not adequately correct this misleading presentation.

Conclusion and Requested Action

Your ad and website fail to reveal material facts regarding important risk information associated with the use of Cubicin in accordance with 21 U.S.C. 321(n), 352(a), (n); 21 C.F.R. 202.1(e)(3)(i). Furthermore, your website suggests that Cubicin is useful in all infections caused by MRSA and MSSA when such has not been demonstrated by substantial evidence or substantial clinical experience and makes an unsubstantiated comparative claim in violation of 21 U.S.C. 201(n), 352(a), (n).

DDMAC requests that Cubist immediately cease the dissemination of violative promotional materials for Cubicin such as those described above. Please submit a written response to this letter on or before August 31, 2004, stating whether you intend to comply with this request, listing all violative promotional materials for Cubicin such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12433 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Cubicin comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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Barbara Chong
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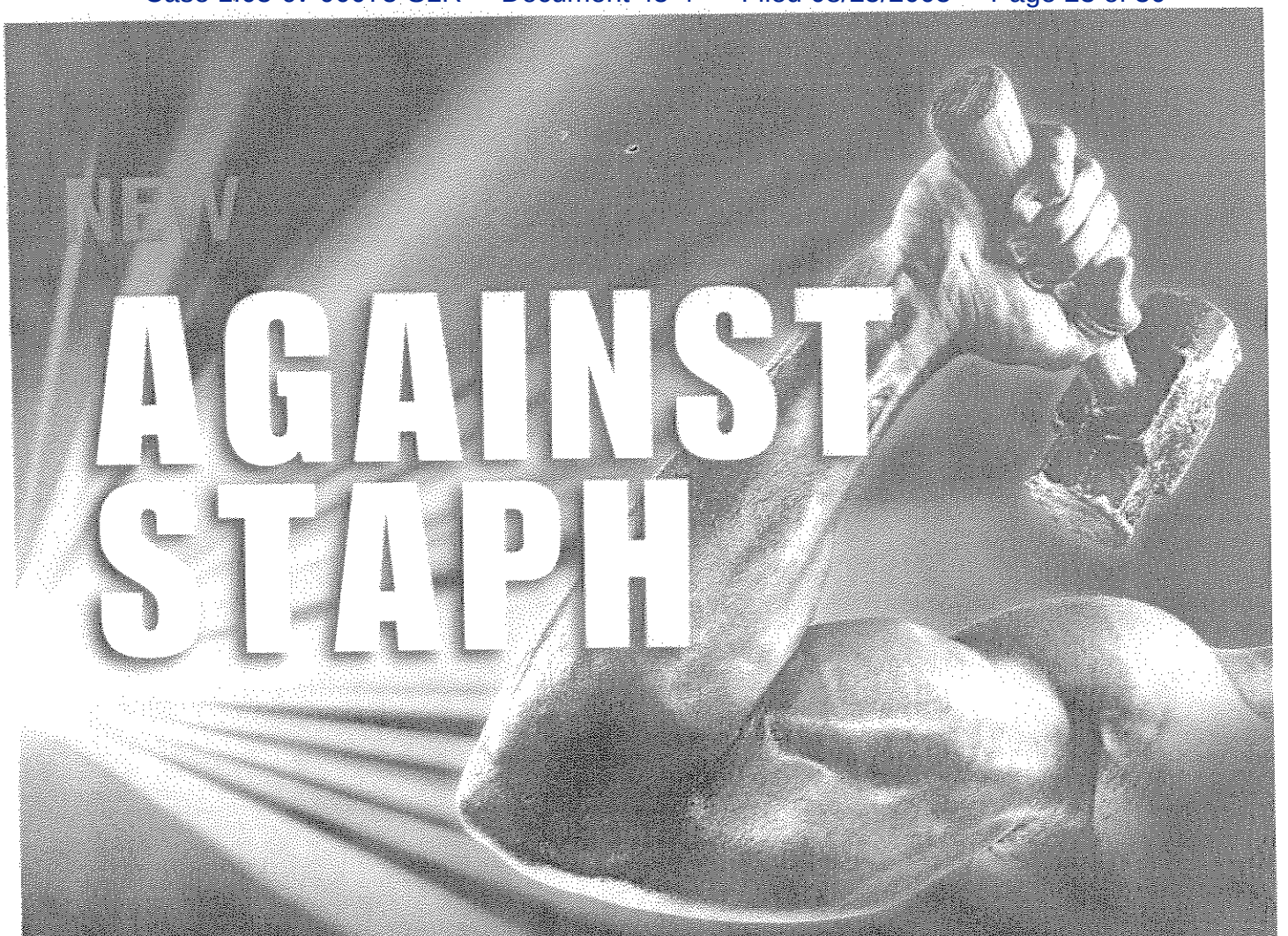

AGAINST STAPH

The only once-daily bactericidal antibiotic—with a distinct mechanism of action—proven effective against both MRSA and MSSA.

Once-A-Day
CUBICIN™
(daptomycin for injection)

CUBICIN is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible strains only).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat or prevent infections caused by bacteria.

CUBICIN is not indicated for the treatment of pneumonia.

Please see brief summary of prescribing information on previous page.

CUBIST

CUBICIN™ (daptomycin for injection)

Brief summary of prescribing information

INDICATIONS AND USAGE

CUBICIN (daptomycin for injection) is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms (see also **DOSAGE AND ADMINISTRATION**): *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* (see subject experience and *Enterococcus faecalis* (vancomycin-susceptible strains only). Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms (see **CLINICAL STUDIES** in full prescribing information).

Daptomycin is not indicated for the treatment of pneumonia.

Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin. Empiric therapy may be initiated while awaiting test results. Appropriate therapy should be adjusted as needed based upon test results.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin.

WARNINGS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including daptomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

If a diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C difficile*.

PRECAUTIONS

General: The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Prescribing CUBICIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Skeletal Muscle: In Phase 3 complicated skin and skin structure infection (cSSSI) trials, elevations in serum creatine phosphokinase (CPK) were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 7/535 (1.3%) comparator-treated patients. Several muscle effects associated with daptomycin were observed in animals (see **ANIMAL PHARMACOLOGY**).

Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. CPK levels should be monitored weekly in patients who receive CUBICIN. Patients who develop unexplained elevations in CPK while receiving daptomycin should be monitored more frequently. Among patients with baseline CPK (≤500 IU), or baseline, 2/19 (10.5%) treated with CUBICIN and 4/24 (16.7%) treated with comparator developed further increases in CPK while on therapy in the same population, no patients developed myopathy. Daptomycin-treated patients with baseline CPK >500 IU (n=19) did not experience an increased incidence of CPK elevations or myopathy relative to those treated with comparator (n=24).

CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevated to >1000 IU (~5x ULN), or in patients without reported symptoms who have marked elevations in CPK (>1000 IU). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving CUBICIN.

In a small number of patients in Phase 1 and Phase 2 studies, administration of CUBICIN was associated with decreases in nerve conduction velocity and with sensory events (eg, paresthesia, hypo- sensory, possibly reflective of peripheral or central neuropathy. Nerve conduction deficits were also detected in a similar number of comparator patients in these studies. In Phase 3 cSSSI and CAP studies, 7/895 (0.7%) daptomycin-treated patients and 7/1018 (0.7%) comparator-treated patients experienced paresthesia. New or worsening peripheral neuropathy was not observed in any of these patients. A similar effect of daptomycin on peripheral nerve was observed (see **ANIMAL PHARMACOLOGY**). Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving CUBICIN.

Drug Interactions: **Warfarin:** Concomitant administration of daptomycin (6 mg/kg once every 24 hours for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug, and the INR was not significantly altered. As experience with the concomitant administration of daptomycin and warfarin is limited to volunteer studies, anticoagulant activity in patients receiving daptomycin and warfarin should be monitored for the first several days after initiating therapy with CUBICIN (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** in full prescribing information).

HMG-CoA Reductase Inhibitors: Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of CPK. There were no reports of skeletal myopathy in a placebo-controlled Phase 1 trial in which 10 healthy subjects receiving simvastatin therapy were treated concurrently with daptomycin (4 mg/kg) once every 24 hours) for 14 days. Experience with co-administration of HMG-CoA reductase inhibitors and CUBICIN is limited; therefore, consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving CUBICIN.

Drug-Laboratory Test Interactions: There are no reported drug-laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of daptomycin. However, neither mutagenic nor clastogenic activities was found in a battery of genotoxicity tests, including the Ames assay, a mammalian cell gene mutation assay, a test for chromosome aberrations in Chinese hamster ovary cells, an *in vivo* micronucleus assay, an *in vitro* DNA repair assay, and an *in vivo* sister chromatid exchange assay in Chinese hamsters.

Daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses up to 150 mg/kg/day, which is approximately 3 times the estimated human exposure (as based upon AUC).

Pregnancy: **Teratogenic Effects: Pregnancy Category B** Reproductive and teratology studies performed in rats and rabbits at doses of up to 75 mg/kg, 3 and 6 times the human dose, respectively, on a body surface area basis, have revealed no evidence of harm to the fetus due to CUBICIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known if daptomycin is excreted in human milk. Caution should be exercised when CUBICIN is administered to a nursing woman.

Pediatric Use: Safety and efficacy of CUBICIN in patients under the age of 18 years old have not been established.

Geriatric Use: Of the 534 patients treated with CUBICIN in Phase 3 complicated clinical trials of complicated skin and skin structure infection, 77 (3% were 65 years of age or older and 12.4% were 75 years or older. In the two Phase 3 clinical studies in patients with cSSSI, lower clinical success rates were seen in patients ≥65 years of age compared to those <65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥65 years old than in patients <65 years of age in both cSSSI studies.

ANIMAL PHARMACOLOGY

In animals, daptomycin administration has been associated with effects on skeletal muscle with no changes in cardiac or smooth muscle. Skeletal muscle effects were characterized by degenerative/regenerative changes and decreased elevations in CPK. No forms of myelopathies were evident in repeat dose studies up to the highest doses tested in rats (150 mg/kg/day) and dogs (100 mg/kg/day). The degree of skeletal myopathy observed on exposure when treatment was extended from 1 month to up to 6 months. Severity was dose dependent. All muscle effects, including microscopic changes, were fully reversible within 30 days following cessation of dosing.

In adult animals, effects on peripheral nerve characterized by axonal degeneration and frequently accompanied by significant losses of caudal reflex, gag reflex, and pain perception were observed at doses higher than those associated with skeletal myopathy. Deficits in the dogs' patellar reflexes were seen within 2 weeks of the start of treatment at 40 mg/kg (2.5 times the human AUC), with some clinical improvement noted within 2 weeks of the cessation of dosing. However, at 75 mg/kg daily for 1 month, 7/8 dogs failed to regain their patellar reflex responses within the duration of a 3 month recovery period. In a separate study in dogs receiving doses of 75 and 100 mg/kg/day for 2 weeks, minimal minimal neurological changes were noted at 6 months after cessation of dosing. However, recovery of peripheral nerve function was evident.

Tissue distribution studies in rats have shown that daptomycin is retained in the kidney but does not appear to penetrate across the blood-brain barrier following single and multiple doses.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Clinical studies sponsored by Cubist enrolled 1435 patients treated with daptomycin and 1185 treated with comparator. Most adverse events reported in these clinical studies were described as mild or moderate in intensity. In Phase 3 cSSSI trials, daptomycin was discontinued in 15/534 (2.8%) patients due to an adverse event while comparator was discontinued in 17/535 (3.0%) patients.

The rate of most common adverse events, organized by body system, observed in cSSSI patients are displayed in the following table.

Incidence (%) of Adverse Events that Occurred in ≥ 2% of Patients in Either Daptomycin or Comparator Treatment Groups in Phase 3 cSSSI Studies

Adverse Event	Daptomycin (N=534)	Comparator* (N=550)
Gastrointestinal disorders		
Constipation	6.2%	6.9%
Nausea	5.4%	9.5%
Diarrhea	5.2%	5.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
General disorders		
Infusion site reactions	5.8%	7.1%
Fever	1.9%	2.5%
Nervous system disorders		
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.5%
Skin/subcutaneous disorders		
Rash	4.3%	3.8%
Pruritis	2.6%	3.8%
Diagnostic investigations		
Abnormal liver function tests	3.0%	1.8%
Elevated CPK	2.8%	1.8%
Infections		
Fungal infections	2.6%	3.2%
Urinary tract infections	2.4%	0.5%
Vascular disorders		
Hypotension	2.4%	1.4%
Hypertension	1.9%	2.5%
Renal/urinary disorders		
Renal failure	2.2%	2.7%
Blood/lymphatic disorders		
Anemia	2.1%	2.5%
Respiratory disorders		
Dyspnea	2.1%	1.6%
Musculoskeletal disorders		
Limb pain	1.9%	2.0%
Arthralgia	0.9%	2.2%

*Comparators included vancomycin (1 g IV q12h) and semi-synthetic penicillins (ie, nafcillin, oxacillin, dicloxacillin, or cloxacillin, 4-12 g/day IV divided doses).

In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS AND USAGE**). Additional adverse events that occurred in 1-2% of patients in either daptomycin- or comparator-treatment groups in the cSSSI studies are as follows: anemia, cellulitis, hypoglycemia, elevated alkaline phosphatase, cough, back pain, abdominal pain, hypotension, hyperglycemia, decreased appetite, anxiety, chest pain, sore throat, cardiac failure, confusion, and Candida infections. These events occurred at rates ranging from 0 to 1.7% in daptomycin-treated patients and at rates of 0.4-1.9% in comparator-treated patients.

Additional drug-related adverse events (possibly or probably related) that occurred in <1% of patients receiving daptomycin in cSSSI trials are as follows:

Body as a Whole: fatigue, weakness, rigors, abdominal distension, flushing, hypersensitivity

Blood/Lymphatic System: leukocytosis, thrombocythemia, eosinophilia, eosinophilia, increased international normalized ratio

Cardiovascular System: supraventricular arrhythmia

Dermatologic System: eczema

Digestive System: abdominal distension, bloating, dyspepsia, pruritus, increased serum lactic dehydrogenase

Metabolic/Nutritional System: hyperglycemia, increased serum creatinine phosphokinase concentrations

Musculoskeletal System: myalgia, muscle cramps, muscle weakness, osteomyelitis

Nervous System: vertigo, mental status change, paresthesia

Special Senses: taste disturbance, eye irritation

Laboratory Changes

Incidence (%) of Creatine Phosphokinase (CPK) Elevations From Baseline While on Therapy in Either Daptomycin or Comparator Treatment Groups in Phase 3 cSSSI Studies

	All Patients				Patients With Normal CPK at Baseline			
	Daptomycin (N=428)		Comparator (N=459)		Daptomycin (N=374)		Comparator (N=392)	
	%	n	%	n	%	n	%	n
No increase	80.7	339	81.7	368	91.2	341	91.1	357
Maximum value >1x ULN*	9.3	40	8.0	41	5.6	25	6.6	35
>2x ULN	4.9	21	4.8	22	2.7	14	3.1	16
>3x ULN	1.4	6	1.6	7	1.1	4	1.0	4
>5x ULN	1.4	6	0.4	2	1.1	4	0.5	2
>10x ULN	0.5	2	0.2	1	0.3	1	0.0	0

*ULN (Upper Limit of Normal) is defined as 200 IU/L

Note: Elevations in CPK observed in patients treated with daptomycin or comparator were not clinically or statistically significantly different (P ≤0.05).

In clinical trials, 0.2% of patients treated with CUBICIN had complaints of muscle pain or weakness associated with CPK elevations greater than 4 times the upper limit of normal. The symptoms resolved within 3 days and CPK returned to normal within 7-10 days after discontinuing treatment (see **PRECAUTIONS, Skeletal Muscle**). In Phase 3 comparator-controlled trials, there was no clinically or statistically significant difference (P ≤0.05) in the frequency of CPK elevations between patients treated with CUBICIN and those treated with comparator. CPK elevations in both groups were generally related to medical conditions, for example, pain and pain associated infection, surgical procedures, or orthopedic injuries, and were not associated with muscle symptoms.

There were no systematic differences between CUBICIN and the comparators in the frequency or distribution of changes in other laboratory parameters, regardless of drug relationship.

OVERDOSAGE

In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is slowly cleared from the body by hemodialysis (approximately 15% recovered over 4 hours) or by peritoneal dialysis (approximately 11% recovered over 48 hours).

DOSAGE AND ADMINISTRATION

Complicated Skin and Skin Structure Infections: CUBICIN 4 mg/kg should be administered over a 30-minute period by intravenous infusion in 0.9% sodium chloride injection once every 24 hours for 7-14 days. Doses of CUBICIN higher than 4 mg/kg/day have not been studied in Phase 3 controlled clinical trials. In Phase 1 and 2 clinical studies, CPK elevations appeared to be more frequent when daptomycin was dosed more frequently than once daily. Therefore, CUBICIN should not be dosed more frequently than once a day.

Because daptomycin is eliminated primarily by the kidney, a dosage modification is recommended for patients with creatinine clearance <30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as listed in the following table. The recommended dosing regimen is 4 mg/kg once every 24 hours for patients with CL_{cr} ≥ 30 mL/min and 4 mg/kg once every 48 hours for CL_{cr} <30 mL/min, including those on hemodialysis or CAPD. When possible, CUBICIN should be administered following hemodialysis on hemodialysis days (see **CLINICAL PHARMACOLOGY** in full prescribing information).

Recommended Dosage of CUBICIN (daptomycin for injection) in Adult Patients With Renal Impairment

Creatinine Clearance	Dosage Regimen
≥30 mL/min	4 mg/kg once every 24 hours
<30 mL/min, including hemodialysis or CAPD	4 mg/kg once every 48 hours

Preparation of Daptomycin for Administration: CUBICIN is supplied in single-use vials containing either 250 or 500 mg daptomycin as a sterile lyophilized powder. The contents of a CUBICIN 250 mg vial should be reconstituted with 5 mL of 0.9% sodium chloride injection. The contents of a CUBICIN 500 mg vial should be reconstituted with 10 mL of 0.9% sodium chloride injection. Reconstituted CUBICIN should be further diluted with 0.9% sodium chloride injection to be administered by intravenous infusion over a period of 30 minutes.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the intravenous solution. Stability studies have shown that the reconstituted solution is stable in the vial for 12 hours at room temperature or up to 48 hours if stored under refrigeration at 2 to 8°C (36 to 46°F). The diluted solution is stable in the infusion bag for 12 hours at room temperature or 48 hours if stored under refrigeration. The combined time vial and infusion bag at room temperature should not exceed 12 hours; the combined time vial and infusion bag under refrigeration should not exceed 48 hours.

CUBICIN vials are for single use only.

Parenteral drug products should be inspected visually for particulate matter prior to administration.

Because only limited data are available on the compatibility of CUBICIN with other intravenous substances, additives or other medications should not be added to daptomycin single-use vials or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed with a compatible solution before and after infusion with daptomycin.

Compatible Intravenous Solutions: CUBICIN is compatible with 0.9% sodium chloride injection and lactated Ringer's injection. CUBICIN is not compatible with solutions containing dextrose.

CUBIST PHARMACEUTICALS

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CUBICIN™
(daptomycin for injection)

- FACTS ABOUT CUBICIN
- FULL PRESCRIBING INFORMATION
- SUSCEPTIBILITY TESTING INFORMATION
- INFECTIOUS DISEASES NEWS
- EVENTS & EDUCATIONAL OPPORTUNITES
- CLINICAL TRIALS

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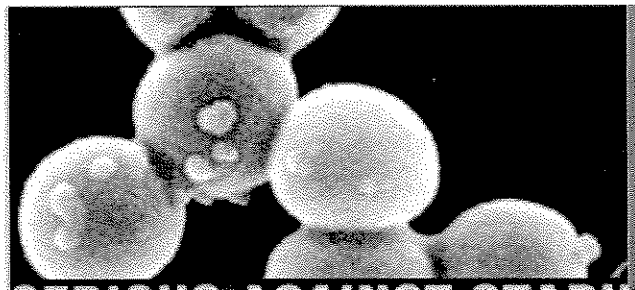
CUBIST PHARMACEUTICALS



SERIOUS AGAINST STAPH

CUBICIN is the only once-daily, rapidly bactericidal antibiotic proven effective against both MRSA and MSSA.

- New class, distinct mechanism of action
- Proven clinically successful against MRSA and MSSA
- Bactericidal against MRSA and MSSA
- Generally well tolerated in clinical trials
- Once a day--the only QD agent approved for treatment of MRSA and MSSA

View our reprint piece [illegible] (PDF, 858k)

NEW ON THE SITE

Welcome to the CUBICIN Web site. Here you can find our package insert and information on susceptibility testing guidelines.

FULL PRESCRIBING INFORMATION

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16 pages (PDF, 328k)

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CUBICIN (daptomycin for injection)

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  - Dosage and Administration
  - Bactericidal Activity
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CUBIST PHARMACEUTICALS

Bactericidal Action

Bactericidal antibiotics are generally regarded as superior to bacteriostatic agents for the treatment of most infections. However, clinical data to support this position are lacking except in specific indications. This slide set highlights the clinical implications of bactericidal versus bacteriostatic antibiotics.

BACTERICIDAL ACTION DOWNLOADS

Download Bactericidal v. Bacteriostatic Slide Kit
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EXHIBIT 10

Compliance Policy Guide
Sec. 120.500
Health Fraud - Factors in Considering Regulatory Action
(CPG 7150.10)

BACKGROUND:

Health Fraud products are articles of unproven effectiveness that are promoted to improve health, well being, or appearance. They can be drugs, devices, foods or cosmetics for human or animal use.

The previous CPG 7150.10 (See Sec. 120.500), Quackery - Priorities for Initiating Legal Action, established agency priorities based on categorizing the violative articles as a "direct health hazard", "indirect health hazard", or "major economic cheat". While such descriptions served the purpose of communicating the general impact of different types of health fraud products on the public, they did not take into account a number of factors which influence the initiation of a regulatory action.

This revision of the CPG establishes practical definitions for "direct health hazard", and "indirect health hazard". Because all health fraud products are in fact economic cheats, a separate definition for major economic cheat has been eliminated. The revised CPG also describes factors the agency will consider prior to initiating regulatory actions against health fraud products.

DEFINITIONS:

HEALTH FRAUD: The deceptive promotion, advertisement, distribution or sale of articles, intended for human or animal use, that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate, or done without adequate knowledge or understanding of the article.

A health fraud product presents a direct health hazard if it is likely to cause injury, death or other serious adverse effect when used as directed or in a customary manner.

A health fraud product presents an indirect health hazard if, as a result of reliance on the product, the consumer is likely to delay or discontinue appropriate medical treatment. The health hazard is indirect when it does no direct harm to the person as a result of its use, but rather denies, delays, or interferes with effective treatment. Consumers who purchase these products are misled by exaggerated or false claims that are made for the products.

POLICY:

Products that pose a direct health hazard to the user shall receive the agency's highest priority attention, regardless of whether they are health fraud products. Documented cases of such products should be expedited and referred to the appropriate center for regulatory follow-up. Health fraud products for which there is not a documented direct health hazard (i.e. indirect health hazard products) will still be considered for regulatory action but on a lower priority.

In evaluating regulatory actions against indirect health hazard products, the following factors should be considered by districts and the centers:

1. Whether the therapeutic claims or conditions to be treated are significant as interpreted by the

appropriate center;

2. Whether there are scientific data or specific information to support the safety or effectiveness of the product for its intended or customary use;

3. The degree of vulnerability of the prospective user group, e.g., the elderly, persons with illnesses for which there is no recognized effective treatment;

4. The availability of other administrative or regulatory alternatives to bring the product or firm into compliance, e.g., education, referral or cooperation with local, state or other federal agencies;

5. The amount of agency resources required and whether they are sufficient to pursue the action to its conclusion;

6. The source of the product, size of the industry distributing the same or similar products, and the impact of the action on that source and industry;

7. The cost of the product, the economic impact of this case on the target user group, as well as the profit (per sale) realized from the sale of the product;

8. The amount (dollar and volume) of product sold, and the geographical scope of its distribution;

In most cases, the seriousness of the therapeutic claims and the nature of the indirect hazard will be obvious. We recognize that when a product with unproven therapeutic claims is first introduced, it is difficult to predict its economic impact because, whether or not a regulatory action is taken, the product may not be accepted in the marketplace. Generally, new health fraud products with undetermined economic impact and limited health significance should result in a *Warning* Letter to the promoter. *Further* regulatory action should be considered for products ** when it appears there is a growing national or substantial regional market for them. The office of compliance in each center will designate a contact and a back-up person for primary consultation on health fraud action.

Foods for human use, nutritional supplements and cosmetics with therapeutic claims will generally be treated as drugs and should be referred to the *CBER or CDER*, Health Fraud Staff, which will coordinate these issues with the Center for Food Safety and Applied Nutrition.

Health fraud products that are the statutory responsibility of another agency should generally be referred to that agency for follow-up. For example, a strictly mail order operation, or one which principally uses media advertising should be referred to the U.S. Postal Service or the Federal Trade Commission and assistance provided, as needed. Local and state health departments and other federal agencies should be consulted because they may be sources of possible corrective action. If the health fraud practice or operation has been legalized (or its practical equivalent) in a certain locality, it is unlikely that a referral for a regulatory action against that practice or operation would be approved in that locality unless there are compelling reasons to do so. This does not preclude action in other jurisdictions. Referral of information on fraudulent products to the appropriate home district and headquarters units should be done as a matter of course.

In general, regulatory action will continue to be deferred on products that are covered by the OTC Review, pending the publication of final monographs.

Material between asterisks is new or revised

Revised: 6/5/87, 3/95